

MONARCAS WEBSITE FOR HEALTH CARE PROVIDERS

INTRODUCTION

The MONARCAS project, *Addressing Lupus Health Disparities Adapting Culturally-Competent Community-Based Education Models Through Local and National Collaborative Partnerships*, seeks to eliminate racial and ethnic health disparities in lupus in communities locally and nationally through a culturally-competent community-based models through partnerships with the Lupus Society of Illinois, Illinois Public Health Association, American College of Rheumatology, and Alliance for Research in Chicagoland Communities (ARCC).

Our previous pilot project, REACH LUPUS, conducted in Chicago's Pilsen community showed that lupus can be devastating in Latinos/Hispanics. Our current project, MONARCAS, aims to expand the same concept. We developed five objectives for sustainability. The first objective is to educate the community residents, patients and families about understanding lupus and its impact using popular opinion leaders (POLs) model. The second objective aims to interact with individuals in community centers in order to improve access to care and coverage for patients with lupus. The third objective is to collaborate with individuals in the community to improve support needed for lupus patients and their families by developing social networks and working with local organizations. The fourth objective aims to expand our experience with Hispanics to the African-American communities in Chicago by introducing the POL program to African-American persons with lupus. The last objective is to disseminate the project at the national level through a workshop to train POLs in other Latino-Hispanic communities nationally in conjunction with the American College of Rheumatology (ACR) and Illinois Public Health Association (IPHA).

DEFINITION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic Lupus Erythematosus (SLE) is an autoimmune, systemic disease of unknown etiology, characterized by antibody formation and immune complex deposition. It can affect any organ system. SLE is described as the greater masquerader because of the diversity of its clinical symptoms. It is characterized by periods of flare-ups (when the disease is active and patients are sick) and periods of remission (when the disease is quiet and patients feel well).

TYPES OF LUPUS ERYTHEMATOSUS

There are five types:

1. **Systemic Lupus erythematosus:** This is the most common type of lupus. It can affect virtually any organ system and presents with a myriad of symptoms that reflect the organ system affected.
2. **Cutaneous Lupus:** There are multiple subsets of this entity:
 - **Acute cutaneous lupus erythematosus (ACLE):** usually accompanies systemic lupus erythematosus manifestations, can present as a malar rash or more diffuse, typically triggered by sun exposure.

- **Subacute cutaneous lupus erythematosus (SCLE):** presents as erythematous and scaly papules, can be annular or psoriasiform. It is highly photosensitive and usually involves sun exposed areas such as arms, chest and back.
- **Discoid lupus:** the most common type of cutaneous lupus, typically itchy and heals with scarring. A small subset of this entity progress to systemic lupus erythematosus.
- **Lupus profundus (panniculitis):** presents as a firm nodule, involves the dermis, often very painful and sometimes heal with fat atrophy seen as skin depression on exam.
- **Other rare forms of cutaneous lupus:**
 - Bullous skin lesions: due to deposition of IgG at the dermal side of the epidermal basement membrane. Can resemble toxic epidermal necrolysis in extreme cases. It should be differentiated from more common bullous lesions such as bullous pemphigoid and dermatitis herpetiformis by getting a skin biopsy.
 - Lupus vasculitis: erythematous non-blanching purpuric lesions involving small size arteries, arterioles and venules.
 - Lupus tumidus: pink to violaceous lesions on sun-exposed areas, heal without scarring.
 - Cutaneous and reticular erythematosus mucinosis: presents as papules filled with mucin, usually on the upper chest and arms.

For more information about cutaneous manifestations of lupus, please refer to Cutaneous lupus erythematosus: issues in diagnosis and treatment. Walling HW, Sontheimer RD. Am J Clin Dermatol. 2009;10(6):365.

3. **Drug induced Lupus erythematosus:** Some medications can trigger autoantibodies production and lupus like symptoms. This phenomenon does not usually cause end organ damage. It typically present as arthritis, skin lesions and serositis. Symptoms tend to resolve after discontinuation of the offending drug. Examples of medications known to induce lupus are: Hydralazine, procainamide, penicillamine and TNF inhibitors.

Please refer to the following article for a list of medications that can cause drug-induced lupus. Drug-induced lupus, Andrea T Borchers Carl L Keen M Eric Gershwin, Annals of the New York Academy of Sciences. , 2007, Vol.1108, p.166-182

4. **Overlap Syndrome/Mixed connective tissue disease:** lupus can overlap with other rheumatic autoimmune diseases such as rheumatoid arthritis, scleroderma or myositis
5. **Neonatal lupus:** This syndrome is seen in infants of mother with positive antibodies to SSA or SSB with or without having symptoms of SLE, Sjogren's or other autoimmune disease. It presents as erythematous macules or plaques over the whole body, more pronounced around the eyes and other photosensitive areas (image 1). The skin lesions usually resolved in the first few months of life since the half-life of anti SSA/SSB antibodies is about 6-8 months. Another characteristic feature of this syndrome is congenital heart block (slow heart beats shortly after birth). When this happens, it is often permanent and needs a pacemaker placement to prevent fatal complications.

ACR CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

{By Tan et al. The revised criteria for the classification of systemic lupus erythematosus. Arthritis rheum 1982; 25(11):1271}

Tan and al. developed the American College of Rheumatology revised criteria for classification of systemic lupus erythematosus in 1982. In 1997, those criteria were updated and the two modifications were made: 1) deleting item 10a (positive LE cell preparation) and 2) changing item 10d to abnormal level of IgG or IgM anticardiolipin antibodies, positive test result for lupus anticoagulant and false positive serologic test for syphilis for at least 6 months. The final updated criteria are as follow:

1. Malar Rash Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis
 1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion

OR

 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder
 1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed

OR

 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder
 1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance

OR

 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance

9. Hematologic disorder

1. Hemolytic anemia--with reticulocytosis

OR

2. Leukopenia--< 4,000/mm³ on ≥ 2 occasions

OR

3. Lymphopenia--< 1,500/ mm³ on ≥ 2 occasions

OR

4. Thrombocytopenia--<100,000/ mm³ in the absence of offending drugs

10. Immunologic disorder

1. Anti-DNA: antibody to native DNA in abnormal titer

OR

2. Anti-Sm: presence of antibody to Sm nuclear antigen

OR

3. Positive finding of antiphospholipid antibodies on:

1. an abnormal serum level of IgG or IgM anticardiolipin antibodies,
2. a positive test result for lupus anticoagulant using a standard method, or
3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test

11. Positive antinuclear antibody An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

The classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is defined as having SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS:

{By Petri m, Orbai am et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis rheum 2012; 64:2677}

SLICC classification criteria are alternative criteria that can be used for SLE clinical care and research. Compared to the ACR classification criteria, SLICC criteria have greater sensitivity but equal to lower specificity.

Clinical and immunologic criteria used in the SLICC classification system:

Clinical criteria:

1. Acute cutaneous lupus, including:
 - Lupus malar rash (do not count if malar discoid)
 - Bullous lupus
 - Toxic epidermal necrolysis variant of SLE
 - Maculopapular lupus rash
 - Photosensitive lupus rash
 - OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus, including:
 - Classic discoid rash
 - Localized (above the neck)
 - Generalized (above and below the neck)
 - Hypertrophic (verrucous) lupus
 - Lupus panniculitis (profundus)
 - Mucosal lupus
 - Lupus erythematosus tumidus
 - Chilblains lupus
 - Discoid lupus/lichen planus overlap
3. Oral ulcers
 - Palate
 - Buccal
 - Tongue
 - OR nasal ulcers
 - in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis or acidic food.
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
 - In the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia.
5. Synovitis involving 2 or more joints, characterized by swelling or effusion
 - OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis
 - Typical pleurisy for more than 1 day
 - OR pleural effusions
 - OR pleural rub
 - Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
 - OR pericardial effusion
 - OR pericardial rub
 - OR pericarditis by electrocardiography
 - In the absence of other causes such as infection, uremia, Dressler's pericarditis.
7. Renal
 - Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours
 - OR red blood cell casts
8. Neurologic
 - Seizures
 - Psychosis
 - Mononeuritis multiplex
 - in the absence of other known causes such as primary vasculitis
 - Myelitis

Peripheral or cranial neuropathy

in the absence of other known causes such as primary vasculitis, infection or diabetes mellitus

Acute confusional state

in the absence of other causes, including toxic/metabolic, uremia, drugs

9. Hemolytic anemia

10. Leukopenia ($\leq 4,000/\text{mm}^3$ at least once)

in the absence of other known cause such as Felty's syndrome, drugs, and portal hypertension

OR

Lymphopenia ($\leq 1,000/\text{mm}^3$ at least once)

in the absence of other known cause such as corticosteroids, drugs, and infection

11. Thrombocytopenia ($\leq 100,000/\text{mm}^3$) at least once

in the absence of other known cause such as drugs, portal hypertension and thrombotic thrombocytopenic purpura

Immunologic criteria

1. ANA level above laboratory reference range

2. Anti-dsDNA antibody level above laboratory reference range (or > 2-fold the reference range if tested by ELISA)

3. Anti-Sm: presence of antibody to Sm nuclear antigen

4. Antiphospholipid antibody positivity as determined by any of the following:

Positive test result for lupus anticoagulant

False-positive test result for rapid plasma reagin

Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)

Positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)

5. Low complement

Low C3

Low C4

Low CH50

6. Direct Coombs' test in the absence of hemolytic anemia

Criteria are cumulative and need not be present concurrently. SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA; ELISA = enzyme-linked immunosorbent assay.

SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a heterogeneous disease with a wide variety of symptoms different from patient to patient. There are multiple ways the disease course can progress: a single flare and then quiescent; alternating flares and remissions, or ongoing activity that never gets better.

Constitutional symptoms

The most common symptom in lupus patients is fatigue and it can persist even when all the other symptoms are controlled. Fever is another common symptom in lupus patients, it is important to differentiate fever from lupus than other causes of fever such as infection (especially when patient are immunosuppressed), malignancy or drug reaction. Lupus patients frequently complain of weight change, either weight loss when disease is active because of poor appetite and pain, or weight gain due to water retention in the case of hypoalbuminemia or due to glucocorticoid use. (see medication section below)

Cutaneous manifestations

Major types of cutaneous lupus	Description of clinical and histological findings
Acute cutaneous lupus erythematosus (ACLE)	
Malar rash (butterfly rash) (image 2)	Fixed erythema over cheeks and nose bridge, typically spares the nasolabial fold. Can be precipitated by sun exposure. Histology: interface dermatitis
Diffuse ACLE (image 3)	Generalized erythematous macules to papules over sun-exposed areas. Histology: similar to malar rash
Subacute cutaneous lupus erythematosus (SCLE)	
Commonly associated with photosensitivity and anti SSA antibodies (image 4)	Small, erythematous and scaly papules, can coalesce to form a polycyclic pattern. Common affected areas: upper extremities and upper chest Histology: vacuolization of the basement membrane and mucus deposition in the dermis.
Chronic cutaneous lupus erythematosus (CCLE)	
Discoid lupus erythematosus (image 5)	Appears initially as erythematous plaques, then extend with inflammatory borders and heals leaving a depressed scar (atrophy) with central hyperpigmentation or depigmentation. Commonly affects scalp, face, back of ears and upper extremities. Histology: hyperkeratosis, follicular plugging, mononuclear cell infiltration at the dermo-epidermal junction.
Less common types of cutaneous lupus are: lupus panniculitis, lupus tumidus and Chilblains.	
Photosensitivity	
Abnormal reaction to ultraviolet light exposure (image 6).	Frequently associated with anti-SSA and anti-SSB antibodies. Can be prevented by avoiding sun exposure and applying sun screen regularly.
Alopecia	
Scarring alopecia (image 7)	A manifestation of chronic discoid lupus in the scalp. Similar clinical and histological findings as described in chronic discoid lupus above.
Non-scarring alopecia	Manifests as thinning of the hair, can be exacerbated by stress or side effects of medications.
Neonatal lupus erythematosus	
Associated with maternal anti-SSA/SSB antibodies	Presents as erythematous macules or plaques with active border, exacerbated by sun

	exposure. Can be associated with congenital heart block, usually permanent.
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Arthritis and arthralgia: common symptom in lupus patients. Arthritis differ from arthralgia by the presence of objective synovitis on physical exam (joint swelling and tenderness to palpation) (image 8). Joint involvement tends to be poly-articular and symmetrical, generally non-erosive and non-deforming.

Renal manifestations: 35% of adults with systemic lupus erythematosus (SLE) have clinical evidence of nephritis at the time of diagnosis in the US and 50 - 60% develop nephritis during the first 10 years of disease [8]. Lupus nephritis is more prevalent in African Americans and Hispanics compared to whites. It is a serious complication of lupus and is a significant cause of morbidity and mortality. It should be screened for on a regular basis to prevent progression and organ damage. Renal involvement in lupus can present with hypertension, hematuria, proteinuria, fluid overload and worsening renal function on blood work.

There are 6 classes of lupus nephritis based on histologic characteristics (proliferation, necrosis, crescents) (image 9):

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of LN:

- Class I Minimal mesangial LN
- Class II Mesangial proliferative LN
- Class III Focal LN (<50% of glomeruli)
 - III (A): active lesions
 - III (A/C): active and chronic lesions
 - III (C): chronic lesions
- Class IV Diffuse LN (≥50% glomeruli)
 - Diffuse segmental (IV-S) or global (IV-G) LN
 - IV (A): active lesions
 - IV (A/C): active and chronic lesions
 - IV (C): chronic lesions
- Class V Membranous LN
- Class VI Advanced sclerosing LN
(≥90% globally sclerosed glomeruli without residual activity)

Indications for kidney biopsy in patients with SLE are listed below:

- Elevation of serum creatinine without obvious explanation.
- Proteinuria ≥1.0 gram per 24 hours (on 24 hour urine collection or spot protein/creatinine ratios).
- Combinations of the following, findings should be confirmed within a short period of time.
 - a. Proteinuria ≥ 0.5 g per 24 hours AND ≥ 5 RBC/hpf
 - b. Proteinuria ≥ 0.5 g per 24 hours AND cellular casts.

For more information, please refer to the following article: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Hahn BH, McMahon MA, Wilkinson A, et al. Arthritis Care Res (Hoboken) 2012; 64:797.

Cardiac manifestations: lupus can affect any layer of the heart including the pericardium, myocardium, or endocardium. The cardiac valves can also be affected. The most common cardiac involvement is pericarditis. Myocarditis and Libman-sacks endocarditis are less common but more severe manifestations. Over the last decade, there have been many studies that looked at the prevalence of coronary artery disease in patients with SLE and showed that patients with SLE are at increased risk for coronary artery disease. Asanuma et al. [9] calculated the coronary artery calcium score in 65 patients with SLE and 69 patients without SLE. They found that calcification was present in 20/65 (31%) of patients with SLE compared to 9/69 (6%) of patients without SLE suggesting an increased prevalence of coronary-artery atherosclerosis in patients with SLE and the reduced age of onset. Please refer to the references below for more detailed information. Schoenfeld et al. [10] study also concluded that atherosclerotic cardiovascular disease risk among SLE patients is at least doubled compared to the general population. This finding was especially significant in young women with SLE compared to their matched controls.

Premature coronary-artery atherosclerosis in systemic lupus erythematosus. Asanuma Y, Oeser A, Shintani AK, et al. N Engl J Med 2003; 349:2407.

The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Schoenfeld SR, Kasturi S, Costenbader KH. Semin Arthritis Rheum 2013; 43:77.

Vascular manifestations: blood vessels can be affected by a variety of mechanisms. Patient can complain of cold intolerance due to vasospastic reaction to cold or emotions known as Raynaud's phenomenon. Lupus can also cause vasculitis most commonly involving the skin but any organ system can be affected. Lupus patients are also at increased risk of thromboembolic events, especially if associated with antiphospholipid antibody syndrome (APLS). (Refer to the section on APLS below)

Gastrointestinal manifestations: Most of gastrointestinal (GI) manifestations in SLE patients are due to medication side effects rather than GI involvement of SLE. In a systematic review of 180 articles from 1965 to 2010 done by Ebert et al. [11], GI manifestations of SLE are very diverse. SLE can affect the vessels of the GI tract causing ulcerations, bleeding, strictures and perforation secondary to bowel ischemia. It can also affect the esophageal muscles causing gastroesophageal reflux like symptoms or dysphagia. Small bowel pseudo-obstruction can present as abdominal pain and vomiting in the setting of active lupus serology. Patient with SLE are prone to salmonella bacteremia presenting as fever and diarrhea. Rarely, SLE can be complicated by protein-losing enteropathy presenting with anasarca, diarrhea and hypoalbuminemia in the absence of nephrotic syndrome. Other less common entities are acute pancreatitis, acute or chronic peritonitis and autoimmune hepatitis. For more information, please refer to the article below:

Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. Ebert EC, Hagspiel KD. J Clin Gastroenterol 2011; 45:436.

Pulmonary manifestations: Lung involvement in patients with SLE can be primary or secondary.

Primary lung disorders	Characteristics
Parenchymal involvement	
Chronic interstitial lung disease	Insidious onset, chronic non-productive cough and progressive dyspnea on exertion.

	<p>Restrictive pattern on pulmonary function tests.</p> <p>High-resolution CT is usually diagnostic, usually correlates with histology (lung biopsy rarely indicated).</p>
Acute pneumonitis	<p>Fever, cough and dyspnea</p> <p>Bibasilar crackles on physical exam</p> <p>Opacities on lung imaging</p> <p>Other causes of pulmonary infiltrates should be excluded, especially infection.</p>
Pleural involvement	<p>Pleuritic chest pain, dyspnea, dry cough.</p> <p>With or without pleural effusion on imaging.</p> <p>Often responds to NSAIDs or corticosteroids.</p>
Vascular involvement	
Diffuse alveolar hemorrhage	<p>Dyspnea, cough, hemoptysis. Can be life-threatening.</p> <p>Bilateral diffuse or patchy opacities on imaging.</p> <p>Broncho-alveolar lavage is diagnostic.</p>
Pulmonary arterial hypertension	<p>Presents with dyspnea on exertion and palpitations. If advanced, it can progress to right-sided heart failure.</p> <p>Mechanism similar to that of idiopathic pulmonary arterial hypertension.</p>
Thromboembolic disease	<p>Can be associated with systemic lupus, especially if co-exists with antiphospholipid syndrome.</p>
Diaphragmatic involvement	<p>Causes the shrinking lung syndrome.</p> <p>Presents with dyspnea and intermittent pleuritic chest pain.</p> <p>Restrictive pattern on pulmonary function tests with no evidence of interstitial or pleural disease on CT.</p>
Secondary lung disorders	
Pulmonary drug toxicity	<p>Presents as acute dyspnea and cough.</p> <p>It should be distinguished from interstitial lung disease and infections.</p>
Lung infections	<p>Very commonly seen in lupus patients in the setting of chronic immunosuppression.</p>

For more details, please refer to the articles below:

Respiratory manifestations of systemic lupus erythematosus: old and new concepts. Pego-Reigosa JM, Medeiros DA, Isenberg DA. *Best Pract Res Clin Rheumatol* 2009; 23:469.

Alveolar hemorrhage in systemic lupus erythematosus: a cohort review. Andrade C, Mendonça T, Farinha F, et al. *Lupus* 2016; 25:75.

Neuropsychiatric manifestations: neuropsychiatric involvement in lupus is very broad. It can affect the central nervous system resulting in strokes, aseptic meningitis, myelitis, seizures or affect the peripheral system resulting in peripheral neuropathies and mononeuritis multiplex. Other manifestations are headaches, delirium and psychosis (should be distinguished from steroid induced psychosis). For more details, please refer to the articles below.

The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42:599.

ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Hanly JG. *Lupus* 2004; 13:861.

Hematologic manifestations: SLE can cause hemolytic anemia, leukopenia, lymphopenia and thrombocytopenia. Because of that, the blood counts should be monitored regularly. Lymphoid organs such as peripheral lymph nodes and spleen are commonly enlarged in patients with active lupus, malignancy should be ruled out prior to attributing them to lupus. For more details, please refer to the articles below.

Hematologic Manifestations of SLE. In: *Lupus Erythematosus: Clinical Evaluation and Treatment*, Schur P, Massarotti E. (Eds), Springer, New York 2012. P. 127-140.

Haematological manifestations of systemic lupus erythematosus. Keeling DM, Isenberg DA. *Blood Rev* 1993; 7:199.

Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Bernatsky S¹, Ramsey-Goldman R, et al. *Ann Rheum Dis*. 2014 Jan; 73 (1):138-42.

DEFINITION OF LUPUS FLARE

The diagnosis of an SLE flare is very challenging and usually controversial because the clinical course of lupus is variable and the disease flares are unpredictable.

Until recently, it has never been a universal definition of lupus flare and this has been a major obstacle to the development of therapies for lupus since the measurement of the outcome of a trial relies on the decrease of number of flares or increase of time to flare. In 2010, a panel of lupus world experts got together and proposed the following definition:

“A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.” The Lupus Foundation of America (LFA) proposes this definition for lupus flare on the basis of its high face validity. *Lupus* (2011) 20, 453-462.

Studies still need to confirm the above definition before it becomes universally adopted.

INITIAL WORK UP OF SYSTEMIC LUPUS ERYTHEMATOSUS

Taking into consideration the common manifestations of systemic lupus, the initial work up should to evaluate markers of disease activity and screen for organ damage to prevent progression.

The complete blood count: detects anemia, leukopenia, lymphopenia and thrombocytopenia.

The complete metabolic panel: evaluates renal, hepatic and metabolic functions.

The urinalysis: detects proteinuria, hematuria and casts.

The partial thromboplastin time screens for the presence of lupus anticoagulant.

Acute phase reactants: like sedimentation rate and C-reactive protein can be elevated when lupus is active.

Joint x-ray: looks for erosions and other bone damage like avascular necrosis.

Electrocardiogram: looks for signs of pericarditis or myocarditis.

Chest x-ray: can show pleural or parenchymal abnormalities.

ANA (antinuclear antibody): if the pre-test probability for lupus is high enough, this test can support the diagnosis if positive.

DsDNA and complement C3 and C4: when the disease is active, DsDNA is usually positive and C3C4 are low because they are consumed.

INTERPRETATION OF POSITIVE ANTINUCLEAR ANTIBODIES (ANA)

Antinuclear antibodies (ANA) are antibodies directed against various components of the cell nucleus. ANA can be positive in many rheumatic diseases as well as healthy people. Therefore, ANA antibodies have a high sensitivity but lack specificity for the diagnosis of lupus. Because of that, the usefulness of ANA is dependent on the pretest probability. Also, patients with negative ANA are unlikely to have lupus.

Besides SLE, ANA antibodies can be present in the majority of rheumatic diseases (like scleroderma, rheumatoid arthritis, juvenile inflammatory arthritis) and other non-rheumatic, autoimmune disease like Hashimoto's thyroiditis. ANA antibodies can be also triggered by infections or chronic illnesses. Its incidence also increases with age and some medication exposure. Interestingly, if a person or a family member has an autoimmune disease, the ANA antibodies can be positive in any member of the family but it does not necessarily mean that the person has an autoimmune disease.

- ANA should be interpreted in context of clinical symptoms
- ANA positive \neq SLE

QUALITY INDICATORS FOR SYSTEMIC LUPUS ERYTHEMATOSUS

{By Yazdany et al. A quality indicator set for systemic lupus erythematosus. *Arthritis & rheumatism* 2009; 61: 370-377}

Quality indicators are useful tools for clinicians caring for patients with SLE. They should not be used as diagnostic criteria but can guide basic work up and management of suspected or confirmed SLE cases. The following questions (Q) and answers (A) can guide primary care physicians providing appropriate care for patients with SLE.

Diagnosis:

Q: If you suspect lupus diagnosis in a patient, what is the initial work-up?

A: ANA, CBC with differential, renal function and urinalysis.

Q: What is the work-up of a newly diagnosed SLE patient?

A: the initial work up should aim to define the disease and possible overlap as well as screen for organ damage. We should check an autoimmune panel including anti-DsDNA, anti-Smith antibody, SSA antibody, SSB antibody, RNP antibody, complement C3 and C4 levels and anti-phospholipid antibodies (anticardiolipin antibody, lupus anticoagulant and Beta2Glycoprotein 1). A complete blood count, a comprehensive metabolic panel and a urinalysis would help screen for organ damage.

General Preventive Strategies:

Q: What can you counsel your SLE patient to prevent flares?

A: Any patient with SLE should be counseled about avoiding sun exposure, wearing protective clothing and applying sunscreens when outdoors. They should also be encouraged to avoid smoking, get sufficient sleep, eat a balanced diet and try to be physically active.

Q: What about vaccines for patients with SLE on immunosuppressive therapy?

A: Patients with SLE should receive age appropriate vaccines as long as they are not live virus vaccines.

Osteoporosis:

Q: Any recommendations for prevention of osteoporosis?

A: Patients with SLE on Prednisone ≥ 7.5 mg/day (or equivalent) for more than 3 months should be on daily supplemental calcium and vitamin D. They should also have a bone density test to screen for osteoporosis.

For patients with SLE on Prednisone ≥ 7.5 mg/day (or equivalent) for more than 1 month and a T-score of -2.5 or less or a history of fragility fracture, a discussion should be held between the physician and the patient regarding starting an anti-resorptive or anabolic therapy, specifically young females given that most of the available therapeutic agents are teratogenic.

Drug Monitoring:

Q: What do I need to know about medications in SLE?

A: Discussion with the patients should take place before any new medication is prescribed for SLE. If a patient with SLE is prescribed a medication, appropriate monitoring for drug toxicity should be documented. In patients with SLE on long term Prednisone, the dose should be tapered to the lowest effective dose to prevent side effects.

Renal Disease:

Q: Any specific recommendations regarding SLE patients with renal disease?

A: If a patient with SLE had evidence of renal involvement within the past 2 years, he/she should be closely monitored every 3 months with a CBC, renal function, urinalysis with microscopic analysis and a quantitative measure of proteinuria.

Q: What is the target blood pressure in SLE patients with renal disease?

A: If an SLE patient with renal disease has two or more blood pressure reading of systolic BP>130 or diastolic BP>80 over 3 months, treatment for hypertension should be started or current regimen should be changed unless patient refuses or a contraindicated.

Q: When should proteinuria be treated?

A: In patients with SLE and evidence of renal disease with proteinuria of 300 mg/day or more and after other causes are ruled out such as infection, diabetes, and drug related nephritis, they should be treated with an ACE inhibitor or an ARB unless patient refuses or contraindicated. Renal biopsy should be considered to confirm the diagnosis if not contraindicated.

Cardiovascular Disease:

Q: What can I do to reduce cardiovascular risk in patients with SLE?

A: Cardiovascular risk factors such as smoking, hypertension, diabetes, obesity and hyperlipidemia should be assessed annually. Please refer to the article below for more details:

Management of cardiovascular complications in systemic lupus erythematosus. Carly Skamra and Rosalind Ramsey-Goldman. Int J Clin Rheumtol. 2010 February 1; 5(1): 75-100.

Pregnancy and Reproductive Health:

Q: What are the facts that I should be aware of while caring for a pregnant patient with SLE?

A: anti-SSA, anti-SSB and anti-phospholipid antibody status should be documented in the patient's chart within 3 years of attempting conception.

Q: How should SLE medications be managed before conception?

A: Any SLE patient between ages 18 and 45 that is started on SLE medications should be offered the appropriate counseling regarding teratogenic risks of medications used to treat SLE such as Methotrexate, Mycophenolate, Leflunamide and Cytoxan. Contraception should be discussed with every patient prior to drug initiation, unless patient had a hysterectomy, oophorectomy, tubal ligation, or post-menopause).

TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

GENERAL TREATMENT CONCEPTS:

Physical activity is extremely important for patients with lupus. Staying active helps with fatigue. Good restorative sleep is also critical to prevent chronic pain commonly associated with lupus.

Lupus patients should be counseled about avoiding smoking because it can exacerbate Raynaud's symptoms as well as joint pain.

Sun exposure can be harmful to patients with lupus. It can cause a photosensitivity rash and even trigger a flare. Patients should be instructed to avoid sun exposure and wear sunscreen every 2 hours when they are outside, even when it is cloudy. The sunscreen should have an SPF of 30 or higher and broad spectrum.

Lupus is highly associated with depression, patients should be screened regularly and referred for counseling if indicated.

PHARMACOLOGIC TREATMENT:

Medications usually used to manage Systemic Lupus Erythematosus are:

NSAIDs: can be used for fever, headache, serositis, arthralgia/arthritis and non-specific pain. Gastro-protection may be considered with chronic use. NSAIDs should be avoided if there is renal involvement or history of hypertension or coronary vascular disease, or on anticoagulants.

Antimalarials: Hydroxychloroquine is approved by Food and Drug Administration (FDA) for SLE. It has disease-modifying properties and is steroid sparing. It is useful in mild disease (skin involvement, fatigue, arthritis), decreases the rate of flares and can prevent end organ damage. It takes up to 12 weeks for it to start working. Hydroxychloroquine is generally safe and well tolerated. It has the potential side effect of causing maculopathy if prescribed for more than 5 years, this potential side effect can be prevented by obtaining annual ophthalmologic examinations.

For more details about mechanism of action of antimalarials, please refer to the reference below:

Reconsidering antimalarials in systemic lupus erythematosus: developments of translational clinical interest. Venuturupalli S, Gudsoorkar V, Wallace D. J Rheumatol 2012; 39:1769.

Corticosteroids: approved by FDA for SLE. Corticosteroids are a critical medication in managing systemic Lupus, used as induction therapy for organ threatening disease. It can be given intravenously, intramuscular, intraarticular or orally. Corticosteroids should be kept at the lowest effective dose necessary to control the disease because of the potential side effects that can result from chronic use like hypertension, diabetes, osteoporosis, cataract, glaucoma, easy bruising, weight gain, hyperlipidemia, cushinoid features, and sleep and mood disorder.

The ultimate goal is to discontinue corticosteroids if possible and use them only as "Steroid rescue" when there is a flare in the form of intramuscular Kenalog or short course oral pills (E.i. Medrol dose pack).

Immunosuppressive therapy is used to treat lupus or to minimize corticosteroid exposure. The immunosuppressants used in lupus are listed below.

Methotrexate: works by inhibiting dehydrofolate reductase. Can be effective for synovitis, constitutional and cutaneous manifestations of lupus. Folic acid should be added to prevent side effects. Common side effects are gastrointestinal intolerance, oral ulcers, headache, bone marrow suppression, transaminitis, pneumonitis and hair thinning. It can be administered orally or subcutaneously. Caution should be taken when prescribing Methotrexate to females in reproductive age because of its teratogenic effect. A thorough pregnancy counseling should always take place before considering this medication in young females.

Leflunomide: is a pyrimidine antagonist, has the same indications as methotrexate. Administered orally. Common side effects are nausea, diarrhea, headache, alopecia, skin rash, transaminitis, cytopenia and respiratory tract infections. It requires frequent blood work monitoring. It should be used with caution in female patients in reproductive age because of its teratogenicity and long half-life (months).

Azathioprine: antimetabolite purine antagonist. Given orally. Can be effective for synovitis, lupus nephritis and hepatic involvement. Case series have demonstrated that it is useful in managing hematologic, pulmonary, muscle and cutaneous manifestations of the disease. Common side effects are gastrointestinal intolerance, transaminitis, bone marrow suppression and allergic reactions. Needs

frequent blood count and liver test monitoring for toxicity, monthly while adjusting the dose, quarterly when on stable dose.

Mycophenolate Mofetil: inhibits inosine monophosphate dehydrogenase which blocks B- and T- cell proliferation. Given orally. Beneficial in most forms of lupus nephritis. It can also be used for non-renal manifestations as a steroid-sparing agent. Its use is limited by gastrointestinal intolerance (nausea, vomiting, diarrhea, abdominal pain). Other less common side effects are opportunistic infections, hypertension, insomnia, headache, hyperglycemia, hypercholesterolemia, leukopenia, anemia, thrombocytopenia and transaminitis. For the reasons listed earlier, it does require frequent blood work monitoring to screen for side effects. Mycophenolate is a category D use in pregnancy. There should be a thorough discussion between health care provider and patient about contraception before starting it and should be stopped 3-6 months before any conception attempt.

Cyclophosphamide: a strong alkylating agent, effective for proliferative and membranous lupus nephritis, central nervous system vasculitis, and serious pulmonary or hematologic manifestations of the disease. Can be administered orally or intravenously. It is a category D use in pregnancy. Common side effects are nausea, diarrhea, abdominal pain, mucositis, stomatitis, opportunistic infections, bone marrow suppression, hair thinning and hair loss, hemorrhagic cystitis and bladder cancer.

Cyclophosphamide can also interfere with fertility by causing premature ovarian failure in females and azoospermia/oligospermia in males. Before prescribing this medication, a detailed discussion about risks and benefits should take place between the physician and the patient. If available, referral to a fertility counselor that can instruct patients about ways to preserve fertility before starting the treatment may be of a significant help. For more details, please refer to the article below:

Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Somers EC¹, Marder W, Christman GM, Ognenovski V, McCune WJ. *Arthritis Rheum*. 2005 Sep; 52 (9):2761-7.

Calcineurin inhibitors: two oral medications commonly used are Cyclosporine and Tacrolimus. The data available currently is insufficient to support their use as induction therapy for severe lupus nephritis but may be used if intolerance to Mycophenolate or Cyclophosphamide. Tacrolimus is preferred due to more favorable toxicity and side effect profile. Blood pressure and serum creatinine should be monitored weekly while adjusting the dose and monthly thereafter. Tacrolimus trough levels can be measured to assess its bioavailability and prevent drug toxicity. An electrocardiogram should be checked before starting this medication because it can cause arrhythmias.

Belimumab: is a monoclonal antibody against one of B-cell survival factors known as BLYS or BAFF. To date, Belimumab is FDA approved for active musculoskeletal and cutaneous symptoms despite being on non-biologic therapy. It is most effective in those with serologic abnormalities. Studies are still ongoing to determine the efficacy of Belimumab in other manifestations of lupus. It is being studied for renal indications. It is available as an IV infusion; SQ dosing currently being tested.

Rituximab: is a B-cell-depleting chimeric antibody targeted against the protein CD20. Rituximab is efficacious in treating thrombocytopenia associated with SLE. The use of Rituximab in lupus nephritis is controversial. Prior studies failed to prove efficacy of Rituximab in lupus nephritis compared with controls. More studies are needed to clarify its use.

ADJUNCTIVE MEASURES: OSTEOPOROSIS AND PREVENTIVE RHEUMATOLOGY

Chronic inflammation from SLE as well as corticosteroid use both cause bone demineralization. For that reason, lupus patients should have bone density screening at regular intervals. Vitamin D level should be checked and replaced if deficient. All patients on chronic corticosteroid use should be on daily calcium and vitamin D. Treatment for osteoporosis should be started if indicated and individualized per

patient. In young females, discussion about potential future pregnancies should take place given the fact that both anti-resorptive and anabolic agents are teratogenic and remain in the body 5 to 10 years after discontinuation. Please refer to the references below for more information.

The American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Jennifer M. Grossman et al. Arthritis Care & Research. Vol. 62, No. 11, November 2010, pp 1515-1526.

Bisphosphonates in patients with autoimmune rheumatic diseases: Can they be used in women of childbearing age? Inès Losada et al. Autoimmunity Reviews. Volume 9, Issue 8, June 2010, Pages 547-552.

Lupus patients have an increased risk of cardiovascular disease compared to the general population. Modifiable cardiovascular risk factors such as hypertension, obesity, diabetes and hyperlipidemia should also be controlled to decrease the incidence of cardiovascular events. Please refer to the articles below for more information.

Premature coronary-artery atherosclerosis in systemic lupus erythematosus. Asanuma Y, Oeser A, Shintani AK, et al. N Engl J Med 2003; 349:2407.

The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Schoenfeld SR, Kasturi S, Costenbader KH. Semin Arthritis Rheum 2013; 43:77.

Patients with lupus are immunocompromised and prone to infections. For that reason, non-live vaccine should be encouraged after their disease is stabilized. Live vaccinations are usually contraindicated in lupus patients. Lupus patients should be advised to get their annual flu shot and pneumonia vaccinations as appropriate.

High dose immunosuppression has been associated with increased risk of opportunistic infections. Prophylactic antibiotics should be considered in certain situations. Please refer to the article below for more information.

Prevention of infection caused by immunosuppressive drugs in gastroenterology. Katarzyna Orlicka. Ther Adv Chronic Dis. 2013 Jul; 4(4): 167-185.

Medication management before and during pregnancy and when lactating:

Medications	Use prior to and during pregnancy	Use when lactating
Corticosteroids	Lowest effective dose	Lowest effective dose
NSAIDs	Discontinue	Discontinue
Aspirin	Low dose if indicated	Low dose if indicated
Azathioprine, cyclosporine, sulfasalazine	Can continue	Azathioprine, cyclosporine: contraindicated Sulfasalazine: can continue
Methotrexate, cyclophosphamide, mycophenolate mofetil, leflunomide.	Discontinue	Discontinue

Hydroxychloroquine	Can continue	Can continue
Warfarin	Switch to unfractionated heparin or low molecular weight heparin	Unclear

The other medications also need to be reviewed, adjusted or discontinued as needed: anti-hypertensive, anti-seizure, anti-depressant, bisphosphonate, lipid lowering therapy.
STOP SMOKING!!!!!!

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

About 1/3 of patients with Lupus have antiphospholipid syndrome (APLS). APLS can occur by itself and does not have to be part of SLE.

The APLS criteria were developed in 1999 and were defined as Sapporo criteria, they were revised by a group in Sydney in 2006. They were mainly developed for research purposes but can be used when trying to make this diagnosis.

The revised Sapporo classification criteria define APLS as a combination of 1 clinical criterion **AND** 1 laboratory criterion by Miyakis and al. (International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Miyakis S, Lockshin MD, Atsumi T, et al. J Thromb Haemost 2006; 4: 295-306.)

- Clinical: The presence of either vascular thrombosis **OR** pregnancy morbidity, defined as follows:
 - Vascular thrombosis event: One or more venous, arterial, or small vessel thrombosis, seen by imaging or found on histology. Superficial venous thrombosis not included.
 - Pregnancy morbidity event: Unexplained fetal death ≥ 10 weeks of gestation of a normal fetus, **OR** ≥ 1 premature birth ≤ 34 weeks of gestation due to eclampsia, preeclampsia, or placental insufficiency, **OR** ≥ 3 unexplained embryonic pregnancy losses ≤ 10 weeks of gestation (*intra-uterine growth restriction can be a clinical manifestation of APLS but is not considered part of the classification criteria*)
- Laboratory - The presence of antiphospholipid antibody (aPL), on ≥ 2 occasions at least 12 weeks apart and no more than five years prior to clinical manifestations, as detailed below:
 - IgG and/or IgM anticardiolipin antibodies (aCL) in moderate or high titer (>40 GPL or MPL units or $>99^{\text{th}}$ percentile for the testing laboratory)
 - Antibodies to beta2-glycoprotein (GP) I of IgG or IgM isotype at a titer $>99^{\text{th}}$ percentile for the testing laboratory.
 - Lupus anticoagulant (LA) activity detected.

FREQUENTLY ASKED QUESTIONS

1. Can Lupus be treated with herbal medicine?

Herbal medications are not approved by the Food and Drug Administration for treatment of any disease. We don't know how they work, therefore we can't recommend any of them. Furthermore, some of them can be harmful and sometimes even fatal. If you want to use an herbal medication or a

supplement, you should discuss the treatment with your physician to review any potential harmful interactions with your prescribed medication or lupus itself.

2. Is pregnancy safe for patients with Lupus

Most patients with lupus can get pregnant but before planning that, their disease should be well controlled for at least 1 years, ideally 2 years. Also, their medications should be adjusted 3-6 months prior to conception to assure that the medications they are on are not harmful for the fetus. Some blood work should to be checked (anti-SSA/SSB antibodies, antiphospholipid antibodies), if the former are positive, the fetus should be monitored closely because he/she is at risk of having a heart block during the pregnancy or shortly after birth; if the latter is positive, the mother is at risk of complications related to the placenta and may need to take anti-platelet or anti-coagulation during pregnancy. These options should be reviewed with your physician team.

3. What methods can be used for contraception in patients with lupus?

The method choice depends on the results of some of the blood work called antiphospholipid antibodies. If some of them are present in high titers, then estrogen containing contraceptives are prohibited. In the rest of the cases, the choice of the contraceptive method should be individualized depending on the situation (barrier, IUD, or hormonal).

4. I have had lupus for 5 years and my symptoms are controlled. Can I come off all medications now?

Even when lupus symptoms are controlled, most patients will need to be on some kind of medications. Getting off all medications may cause your disease to flare up and relapse again. You should talk to your rheumatologist about your situation and together you can make a decision. Stopping all your medications without consulting your rheumatologist is strongly discouraged.

5. I was recently diagnosed with lupus and feel very uncomfortable disclosing this news to my family and friends. As a result, I feel isolated and starting to feel depressed. What should I do?

Your situation is one of the most common ones we encountered in our daily practice. Being diagnosed with lupus is nothing to be ashamed of. It is not your fault. It is an autoimmune disease like type I diabetes that affect children. It is not infectious, nor contagious. There are several support groups that are there to help people recently diagnosed with lupus like you to cope with their new life and try to maintain the best quality of life possible. Depression is very commonly encountered in people with lupus. If you feel depressed, you should not hesitate to discuss that with your rheumatologist or primary care physician so that they can refer you to the appropriate specialist. The more you learn about lupus and how it affects you, the better you can partner with your healthcare providers in managing your disease.

For more frequently asked questions, please refer to the website below:

<http://www.lupusil.org/rush-university-medical-center-doctors-answer-lupus-questions.html>

CME LINK THROUGH LUPUS SOCIETY OF ILLINOIS (LSI)

You can learn more about SLE and earn CME credits through the Lupus Society of Illinois at

<http://www.lupusil.org>

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RESOURCES FOR THE PATIENTS

1. Lupus society of Illinois. <http://www.lupussil.org>
2. American College of Rheumatology. <http://www.rheumatology.org>
3. Lupus Foundation of America. <http://www.lupus.org>
4. Lupus Research institute. <http://www.lupusresearchinstitute.org>
5. The lupus initiative website. <http://www.thelupusinitiative.org>

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PICTURES:

Image 1: Neonatal lupus:



Image 2: malar rash



Image 3: diffuse acute cutaneous lupus:



Image 4: Subacute cutaneous lupus:



Image 5: Chronic cutaneous lupus:



Image 6: Photosensitivity:



Image 7: Scarring alopecia:



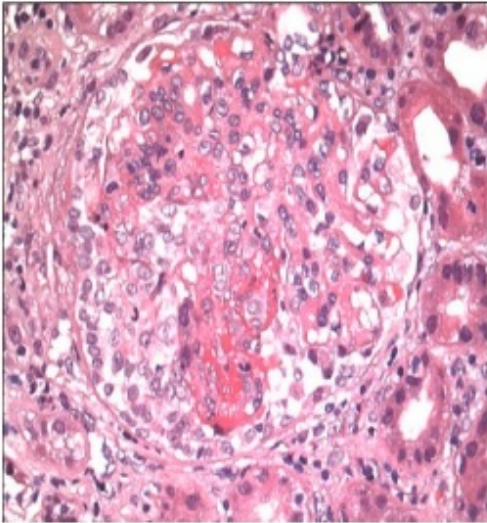
Image 8: Synovitis:



Image 9: Lupus nephritis: renal biopsy

Lupus Nephritis(Biopsy Findings)

Proliferative GN with necrosis



Cellular Crescent

